

Claims

1           1. A method for making a water insoluble  
2 biocompatible composition, said method comprising combining,  
3 in an aqueous mixture, a polyanionic polysaccharide, a  
4 nucleophile, and an activating agent under conditions  
5 sufficient to form said composition.

6           2. The method of claim 1 wherein two or more  
7 polyanionic polysaccharides are employed.

8           3. The method of claim 1 or 2 wherein said  
9 polyanionic polysaccharides are chosen from the group  
10 consisting of carboxymethyl cellulose, carboxymethyl  
11 amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin  
12 sulfate, heparin, and heparin sulfate.

13           4. The method of claim 1 wherein said polyanionic  
14 polysaccharide is hyaluronic acid.

15           5. The method of claim 1 wherein said polyanionic  
16 polysaccharide is carboxymethyl cellulose.

17           6. The method of claim 1 wherein said polyanionic  
18 polysaccharide is carboxymethyl amylose.

19           7. The method of claim 2 wherein two of said  
20 polyanionic polysaccharides are hyaluronic acid and  
21 carboxymethyl cellulose.

22           8. The method of claim 1 wherein said activating  
23 agent is chosen from the group consisting of benzotriazole-  
24 1-yloxytris(dimethylamino)phosphonium hexafluorophosphate,  
25 O-benzotriazole-1-yl-N,N,N',N'-tetramethyluronium

26 hexafluorophosphate, bromotris(dimethylamino)phosphonium  
27 hexafluorophosphate, bromotris(pyrrolidinyl)phosphonium  
28 hexafluorophosphate and the corresponding halide salts  
29 thereof.

30 9. The method of claim 1 wherein said polyanionic  
31 polysaccharide are present in a concentration of 0.0002 -  
32 0.1M.

33 10. The method of claim 9 wherein said polyanionic  
34 polysaccharide is present in a concentration of 0.0005 -  
35 0.02M.

36 11. The method of claim 1 wherein said method is  
37 carried out at a pH 3.5 - 8.0.

38 12. The method of claim 1 wherein the stoichiometry  
39 of said activating agent to said polysaccharide is at least  
40 0.1 molar equivalent of said activating agent per molar  
41 equivalent of said polyanionic polysaccharide.

42 13. The method of claim 1 wherein said nucleophile  
43 is chosen from the group consisting of an amino acid amide,  
44 a monofunctional amine, an amino acid ester, an amino  
45 alcohol, an amino thiol, an amino phenol, an amino catechol,  
46 an amino acid, a salt of an amino acid, a peptide, and a  
47 protein.

48 14. The method of claim 1 wherein the stoichiometry  
49 of said polyanionic polysaccharide to said nucleophile is at  
50 least 1 molar equivalent of nucleophile per molar equivalent  
51 of polyanionic polysaccharide.

52           15. A method for making a water insoluble  
53 biocompatible composition, said method comprising combining,  
54 in an aqueous mixture, one or more polyanionic  
55 polysaccharides, a modifying compound, a nucleophile, and an  
56 activating agent under conditions sufficient to form said  
57 composition wherein said modifying compound causes the  
58 formation of a new active carbonyl groups on said  
59 polyanionic polysaccharide.

60           16. The method of claim 15 wherein two or more  
61 polyanionic polysaccharides are employed.

62           17. The method of claim 15 or 16 wherein said  
63 polyanionic polysaccharides are chosen from the group  
64 consisting of carboxymethyl cellulose, carboxymethyl  
65 amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin  
66 sulfate, heparin, and heparin sulfate.

67           18. The method of claim 15 wherein said polyanionic  
68 polysaccharide is hyaluronic acid.

69           19. The method of claim 15 wherein said polyanionic  
70 polysaccharide is carboxymethyl cellulose.

71           20. The method of claim 15 wherein said polyanionic  
72 polysaccharide is carboxymethyl amylose.

73           21. The method of claim 16 wherein two of said  
74 polyanionic polysaccharides are hyaluronic acid and carboxyl  
75 methyl cellulose.

76           22. The method of claim 15 wherein said modifying  
77 compound is chosen from the group consisting of

78 1-hydroxybenzotriazole hydrate, 1-hydroxybenzotriazole  
79 monohydrate, N-hydroxysulfosuccinimide,  
80 N-hydroxysuccinimide, 4-nitrophenol, 2-nitrophenol,  
81 4-nitrothiophenol, 2-nitrothiophenol, pentachlorophenol,  
82 pentafluorophenol, imidazole, tetrazole, and  
83 4-dimethylaminopyridine.

84           23. The method of claim 15 wherein said activating  
85   agent comprises a carbodiimide.

86           24. The method of claim 23 wherein said  
87 carbodiimide comprises 1-ethyl-3-(3-dimethylaminopropyl)  
88 carbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl)  
89 carbodiimide methiodide.

25. The method of claim 15 wherein said polyanionic polysaccharide is present in a concentration of 0.0002 - 0.1M.

26. The method of claim 25 wherein said polyanionic polysaccharide is present in a concentration of 0.0005 to 0.02M.

96            27. The method of claim 15 wherein said method is  
97 carried out at a pH 3.5 - 8.0.

98           28. The method of claim 15 wherein the  
99   stoichiometry of said polyanionic polysaccharide to said  
100   activating agent is at least 0.1 molar equivalent of said  
101   activating agent per molar equivalent of said polyanionic  
102   polysaccharide.

103           29. The method of claim 15 wherein the  
104 stoichiometry of said modifying agent to said activating  
105 agent is at least 1 molar equivalent of said modifying  
106 compound per molar equivalent of said activating agent.

107           30. The method of claim 15 wherein said nucleophile  
108 is chosen from the group consisting of an amino acid amide,  
109 a monofunctional amine, an amino acid ester, an amino  
110 alcohol, an amino thiol, an amino phenol, an amino catechol,  
111 an amino acid, a salt of an amino acid, a peptide, and a  
112 protein.

113           31. A water insoluble composition prepared  
114 according to the method of claim 1, 2, 15 or 16.

115           32. The composition of claim 31 wherein said  
116 composition is in the form of a gel.

117           33. The composition of claim 31 wherein said  
118 composition is in the form of fibers.

119           34. The composition of claim 31 wherein said  
120 composition is in the form of a membrane.

121           35. The composition of claim 31 wherein said  
122 composition is in the form of a foam.

123           36. The composition of claim 31 wherein said  
124 composition is in the form of an adhesion prevention  
125 composition.

126 37. The composition of claim 31, further comprising  
127 a pharmaceutically active substance dispersed within said  
128 composition.

129 38. The composition of claim 37 wherein said  
130 pharmaceutically active substance is chosen from the group  
131 consisting of proteins, growth factors, enzymes, drugs,  
132 biopolymers, and biologically compatible synthetic polymers.

133 39. A water insoluble composition comprising the  
134 reaction product of a polyanionic polysaccharide, a  
135 nucleophile, and an activating agent.

136 40. A water insoluble composition comprising the  
137 reaction product of two or more polyanionic polysaccharides,  
138 a nucleophile, and an activating agent.

139 41. The water insoluble composition of claim 39 or  
140 40 wherein said activating agent is chosen from the group  
141 consisting of benzotriazole-1-yloxytris(dimethylamino)-  
142 phosphonium hexafluorophosphate, O-benzotriazole-1-yl-  
143 N,N,N',N'-tetramethyluronium hexafluorophosphate,  
144 bromotris(dimethylamino)phosphonium hexafluorophosphate,  
145 bromotris(pyrrolidinyl)phosphonium hexafluorophosphate and  
146 the corresponding halide salts thereof.

147 42. A water insoluble composition comprising the  
148 reaction product of a polyanionic polysaccharide, a  
149 modifying compound, a nucleophile, and an activating agent.

150 43. A water insoluble composition comprising the  
151 reaction or product of two or more polyanionic  
152 polysaccharides, a modifying compound, a nucleophile, and an  
153 activating agent.

154 44. The composition of claim 39, 40, 42 or 43  
155 wherein said polyanionic polysaccharides are chosen from the  
156 group consisting of carboxymethyl cellulose, carboxymethyl  
157 amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin  
158 sulfate, heparin, and heparin sulfate.

159 45. The composition of claim 39 or 42 wherein said  
160 polyanionic polysaccharide is hyaluronic acid.

161 46. The composition of claim 39 or 42 wherein said  
162 polyanionic polysaccharide is carboxymethyl cellulose.

163 47. The composition of claim 39 or 42 wherein said  
164 polyanionic polysaccharide is carboxymethyl amylose.

165 48. The composition of claim 40 or 43 wherein two  
166 of said polyanionic polysaccharides are hyaluronic acid and  
167 carboxy methyl cellulose.

168 49. The composition of claim 39, 40, 42 or 43  
169 wherein said nucleophile is chosen from the group consisting  
170 of an amino acid amide, a monofunctional amine, an amino  
171 acid ester, an amino alcohol, an amino thiol, an amino  
172 phenol, an amino catechol, an amino acid, a salt of an amino  
173 acid, a peptide, and a protein.

174 50. The composition of claim 42 or 43 wherein said  
175 modifying compound is chosen from the group consisting of  
176 1-hydroxybenzotriazole hydrate, 1-hydroxybenzotriazole  
177 monohydrate, N-hydroxysulfosuccinimide,  
178 N-hydroxysuccinimide, 4-nitrophenol, 2-nitrophenol,

179 4-nitrothiophenol, 2-nitrothiophenol, p ntachlorophenol,  
180 pentafluorophenol, imidazole, tetrazole, and  
181 4-dimethylaminopyridine.

182 51. The composition of claim 42 or 43 wherein said  
183 activating agent comprises a carbodiimide.

184 52. The composition of claim 51 wherein said  
185 carbodiimide comprises 1-ethyl-3-(3-dimethylaminopropyl)  
186 carbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl)  
187 carbodiimide methiodide.

188 53. The composition of claims 39, 40, 42 or 43  
189 wherein said composition is in the form of a gel.

190 54. The composition of claims 39, 40, 42 or 43  
191 wherein said composition is in the form of fibers.

192 55. The composition of claims 39, 40, 42 or 43  
193 wherein said composition is in the form of a membrane.

194 56. The composition of claims 39, 40, 42 or 43  
195 wherein said composition is in the form of a foam.

196 57. The composition of claims 39, 40, 42 or 43  
197 wherein said composition is in the form of an adhesion  
198 prevention composition.

199 58. The composition of claims 39, 40, 42 or 43,  
200 further comprising a pharmaceutically active substance  
201 dispersed within said composition.



202 ~~59. The composition of claim 58 wherein said~~  
203 ~~pharmaceutically active substance is chosen from the group~~  
204 ~~consisting of proteins, growth factors, enzymes, drugs,~~  
205 ~~biopolymers, and biologically compatible synthetic polymers.~~